

Claims

1. An agent for prevention and/or treatment of itching, which comprises, as an active ingredient, a substance capable of suppressing the function involved in signal transduction of a protein having the amino acid sequence represented by SEQ ID NO: 11.

2. An agent for prevention and/or treatment of itching, which comprises one of the following 1) to 4) as an active ingredient:

1) an oligonucleotide having a sequence complementary to that of oligonucleotide comprising continuous 5 to 60 nucleotides selected from the nucleotide sequence represented by SEQ ID NO: 12 or a derivative of said oligonucleotide,

2) an oligonucleotide having a sequence complementary to that of oligonucleotide comprising continuous 5 to 60 nucleotides selected from the nucleotide sequence represented by SEQ ID NO: 14 or a derivative of said oligonucleotide,

3) an oligonucleotide having a sequence complementary to that of oligonucleotide comprising continuous 5 to 60 nucleotides selected from the nucleotide sequence represented by SEQ ID NO: 18 or a derivative of said oligonucleotide, and

4) an oligonucleotide comprising 5 to 60 nucleotides which hybridizes under stringent conditions with DNA having the nucleotide sequence represented by one member selected from

SEQ ID NOs: 12, 14 and 18 and which is capable of suppressing the function involved in signal transduction of a protein having the amino acid sequence represented by SEQ ID NO: 11 or a derivative of said oligonucleotide.

3. An agent for prevention and/or treatment of itching, which comprises one of the following 1) to 4) as an active ingredient:

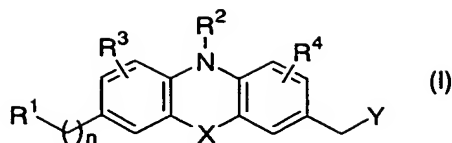
1) an antibody which recognizes a protein having the amino acid sequence represented by SEQ ID NO: 11,

2) an antibody which recognizes a protein having the amino acid sequence represented by SEQ ID NO: 13,

3) an antibody which recognizes a protein having the amino acid sequence represented by SEQ ID NO: 17, and

4) an antibody, which recognizes a protein having the amino acid sequence in which one or more amino acid(s) is/are deleted, substituted or added in the amino acid sequence represented by one member selected from SEQ ID NOs: 11, 13 and 17 and which has the function involved in signal transduction of a protein having the amino acid sequence represented by SEQ ID NO: 11.

4. A nitrogen-containing tricyclic compound represented by the formula (I) or a quaternary ammonium salt thereof, or a pharmaceutically acceptable salt thereof;



[wherein R^1 represents a substituted or unsubstituted heterocyclic group, $-NR^5R^6$ (wherein R^5 and R^6 are the same or different and each represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aralkyl or substituted or unsubstituted heterocyclic alkyl, or R^5 and R^6 are combined together with the adjacent nitrogen atom to form a substituted or unsubstituted heterocyclic group), $-OR^7$ (wherein R^7 represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkanoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl or substituted or unsubstituted heterocyclic alkyl), $-SR^{7a}$ (wherein R^{7a} has the same meaning as the above R^7), $-CONR^{5a}R^{6a}$ (wherein R^{5a} and R^{6a} have the same meanings as the above R^5 and R^6 , respectively), $-CO_2R^{7b}$ (wherein R^{7b} has the same meaning as the above R^7), $-N^+R^{5b}R^{6b}R^8$ (wherein R^{5b} and R^{6b} have the same meanings as the above R^5 and R^6 , respectively, and R^8 represents lower alkyl, lower alkenyl or aralkyl), formyl, carboxy or

cyano;

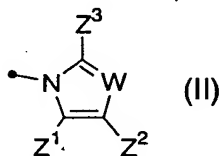
R^2 represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aralkyl or substituted or unsubstituted heterocyclic alkyl;

R^3 and R^4 are the same or different and each represents hydrogen, lower alkyl or halogen;

n represents 0 or 1;

X represents $-(CH_2)_2-$ or $-CH=CH-$; and

Y represents the formula (II);



(wherein W represents CH or a nitrogen atom;

Z^1 and Z^2 are the same or different and each represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl or substituted or unsubstituted heterocyclic alkyl, or Z^1 and Z^2 are combined together with two carbon atoms being adjacent to each of them to form a substituted or unsubstituted aromatic ring or substituted or unsubstituted heterocycle; and

Z^3 represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted aryl, a substituted or unsubstituted heterocyclic group, substituted or unsubstituted aralkyl or substituted or unsubstituted heterocyclic alkyl)].

5. The nitrogen-containing tricyclic compound or the quaternary ammonium salt thereof, or the pharmaceutically acceptable salt thereof according to claim 4, wherein R^1 is $-NR^5R^6$ and R^5 and R^6 are combined together with the adjacent nitrogen atom to form a substituted or unsubstituted heterocyclic group.

6. The nitrogen-containing tricyclic compound or the quaternary ammonium salt thereof, or the pharmaceutically acceptable salt thereof according to claim 4 or 5, wherein R^2 is hydrogen.

7. The nitrogen-containing tricyclic compound or the quaternary ammonium salt thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 4 to 6, wherein R^3 and R^4 are hydrogen.

8. The nitrogen-containing tricyclic compound or the quaternary ammonium salt thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 4 to 7, wherein Z^1 and Z^2 are combined together with two carbon atoms

being adjacent to each of them to form substituted or unsubstituted heterocycle.

9. A pharmaceutical composition comprising the nitrogen-containing tricyclic compound or the quaternary ammonium salt thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 4 to 8 as an active ingredient.

10. An agent for prevention and/or treatment of itching comprising the nitrogen-containing tricyclic compound or the quaternary ammonium salt thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 4 to 8 as an active ingredient.

11. A suppressor of the function involved in signal transduction of a protein having the amino acid sequence represented by SEQ ID NO: 11, comprising the nitrogen-containing tricyclic compound or the quaternary ammonium salt thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 4 to 8 as an active ingredient.

12. A method for screening a therapeutic agent for itching, which comprises the following steps 1) to 4):

1) the step where sphingosyl phosphorylcholine (SPC) is subcutaneously and intracutaneously administered to a mammal except a human being so that scratching behavior in the mammal except a human being is induced,

2) the step where numbers of scratching behavior in the mammal except a human being induced by SPC in the presence or absence of the test compound are measured,

3) the step where numbers of scratching behavior in the mammal except a human being induced by SPC in the presence of the test compound and in the absence of the test compound are compared, and

4) the step where a substance which decreases the number of scratching behavior induced by SPC is selected from test compounds.

13. A method for prevention and/or treatment of itching, which comprises administering an effective amount of the nitrogen-containing tricyclic compound or the quaternary ammonium salt thereof, or the pharmaceutically acceptable salt thereof described in any one of claims 4 to 8.

14. Use of the nitrogen-containing tricyclic compound or the quaternary ammonium salt thereof, or the pharmaceutically acceptable salt thereof described in any one of claims 4 to 8 for the manufacture of an agent for prevention and/or treatment of itching.

15. The agent for prevention and/or treatment of itching according to any one of claims 1 to 3 and 10, wherein the itching is that which is accompanied by a disease selected from a skin disease, a liver/biliary tract disease, a renal disease, an endocrinal/metabolic disease, a blood disease, a malignant

tumor, a nerve disease and AIDS.

16. The agent for prevention and/or treatment of itching according to claim 15, wherein the itching is that accompanied by skin disease and said skin disease is that selected from atopic dermatitis, eczema/dermatitis, urticaria, pruritus, xeroderma, bite, scabies, fungal infection, skin itching, hypertrophic cicatrix, psoriasis, blister and drug eruption.

17. A method for prevention and/or treatment of itching, which comprises administering a therapeutically effective amount of a substance capable of suppressing the function involved in signal transduction of a protein having the amino acid sequence mentioned in SEQ ID NO: 11..

18. A method for prevention and/or treatment of itching, which comprises administering a therapeutically effective amount of an oligonucleotide or a derivative of said oligonucleotide which is any one of 1) to 4) described in claim 2.

19. A method for prevention and/or treatment of itching, which comprises administering a therapeutically effective amount of an antibody which is any one of 1) to 4) described in claim 3.

20. Use of a substance capable of suppressing the function involved in signal transduction of a protein having the amino acid sequence represented by SEQ ID NO: 11 for the manufacture of an agent for prevention and/or treatment of

itching.

21. Use of an oligonucleotide or a derivative of said oligonucleotide which is any one of 1) to 4) described in claim 2 for the manufacture of an agent for prevention and/or treatment of itching.

22. Use of an antibody which is any one of 1) to 4) described in claim 3 for the manufacture of an agent for prevention and/or treatment of itching.